Remarks

Claims 1-4, 22-26, 41, 42 and 59-71 are pending. By this amendment, claims 72-74 would be added, and claims 64, 70 and 71 cancelled without prejudice. Therefore, claims 1-4, 22-26, 41, 42, 59-63, 65-69, and 72-74 would be pending upon entry of this amendment.

Support for the new claims can be found throughout the specification, for example:

Claims 72-73: claims 1, 59 and 65.

Claim 74: page 72, line 21

Therefore, no new matter is added by this amendment. In addition, no amendments were made due to distinguish prior art.

35 U.S.C. § 112, first paragraph, written description

Claims 68-71 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. It is asserted in the Office action that these claims contain new matter. Applicants respectfully disagree and request reconsideration. Even if there is no "literal support" for a method of administering an amount of EDA1-II that is the C-terminal 240 or 211 amino acids or in which E294 has been substituted to a tissue sufficient to promote either hair follicle development, tooth development or sweat gland development, this does not render the language new matter. Indeed, the MPEP states that to satisfy the written description requirement, *ipsis verbis* support (in the same words) is not required for the description to be sufficient. (MPEP§ 2163)

The application does provide the requisite support for the language used in claims 68-71. For example, on page 22, lines 12-18, it is noted that EDA1-II can be mutated at E294, and that assays can be "used to determine whether the mutant peptide retains EDA1-II biological activity, as described in EXAMPLES 19 and 20." Examples 19 and 20 (starting on page 50), disclose administration of EDA1-II proteins and nucleic acids (including variants or fragments thereof, which would thus include those EDA1-II peptides mutated at E294 or the C-terminal 240 or 211 amino acids of EDA1-II) to subjects to promote hair follicle development, tooth development or sweat gland development. Because the specification provides the requisite support for a method of administering an amount of EDA1-II that is the C-terminal 240 or 211 amino acids or in which E294 has been substituted to a tissue sufficient to promote either hair

follicle development, tooth development or sweat gland development, Applicants request that the rejection be withdrawn.

Applicants thank the Examiner for withdrawing the 35 U.S.C. § 112, first paragraph, written description rejection of claims 59-63.

Claims 64, 70 and 71 continue to be rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Although Applicants respectfully disagree, in order to expedite prosecution, these claims have been cancelled without prejudice to prosecution in a future application.

35 U.S.C. § 112, first paragraph, enablement

All of the pending claims continue to be rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Office action recites the factors from *In re Wands*, and concludes that it would require undue experimentation for one skilled in the art to make and use the claimed invention based on the disclosure and information known in the art. Applicants respectfully disagree and request reconsideration.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. As shown by the data presented in the enclosed Rule 132 Declaration, those skilled in the art can practice the method of the pending claims using the teachings in the application, coupled with standard molecular biology techniques.

Based on the teachings and methods provided in the present application, Dr. Pascal Schneider's laboratory conducted experiments and has demonstrated that intraperitoneal administration of 10-20 μg (10-20 mg/kg) of a purified fragment of the human EDA protein (amino acids 239-391) to newborn EDA-deficient (*Tabby*) mice induces the formation of hair on the tail. This data addresses the concern on page 14 of the Office action that there was no data showing that the effects of EDA1-II can be demonstrated in the actual subject injected. That amino acids 239-391 of EDA1-II can be used to increase hair follicle development by is disclosed throughout the application (for example see page 16, line 29 – page 17 line 2;

page 21, lines 21-25; and page 50, lines 21-24). That the protein can be introduced intraperitoneally is disclosed on page 72, line 22 and line 32. The dosage of protein administered falls within the range provided in the specification on page 15, lines 4-12 (0.01 mg/kg to about 1 g/kg body weight). Therefore, the present application provides sufficient teaching to enable one skilled in the art such as Dr. Schneider to practice the claimed method.

The *Tabby* mouse disclosed throughout the specification, and used by Dr. Schneider, is the accepted mouse model for the human disease ectodermal dysplasia. The demonstrated ability of increasing EDA1-II activity to stimulate hair growth in a subject having an ectodermal disorder (such as the *Tabby* mouse), provides guidance for the application of EDA1-II to humans for the treatment of ectodermal dysplasia. As stated in Paragraph 3 of Dr. Schneider's Rule 132 Declaration, the success of treatment of *Tabby* mice is accepted by those of skill in the art to correlate with results in humans.

In summary, the present application provides detailed teachings which enable those skilled in the art to practice the claimed method of increasing development of an ectodermal structure. In view of this data, one skilled in the art would expect that administration of an EDA1-II protein (or a fragment, variant, or fusion thereof that retains EDA1-II biological activity) to a subject (including human subjects) having an ectodermal disorder would increase growth of ectodermal structures, such as hair. Because "data from in vitro or animal testing is generally sufficient to support therapeutic utility" (MPEP § 2107.3), the present claims satisfy the enablement requirement, as data is presented showing a favorable result using the claimed method in a laboratory animal. In view of the arguments and Rule 132 Declaration presented herein, Applicants request that the 35 U.S.C. § 112, first paragraph rejections be withdrawn.

In view of these amendments, and the enclosed Rule 132 Declaration, this amendment places the application in condition for allowance, and Applicants request that it be entered. If there are any minor issues that need to be resolved prior to issuing a Notice of Allowance, the Examiner is invited to telephone the undersigned.

Respectfully submitted,

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EDUCATION AND POSITIONS HELD

2002-present	Assistant Professor, at the Department of Biochemistry, University of Lausanne, Switzerland. Research project: " TNF family members APRIL, BAFF and EDA". Recipient of stipends from the Federal Office of Public Health (1996-2000) and the FNRS (2000-2005). Co-applicant of a NCCR grant (2001-2003) and of a CTI grant (2004-2006).
2001	Privat-Docent, University of Lausanne
1994-2002	Research Assistant at the Institute of Biochemistry, University of Lausanne. Group of Prof. J. Tschopp. Research project: " Apoptosis-inducing ligands and receptors".
1992-1994	Post-doctoral long-term EMBO fellow, Department of Biochemistry, University of Dundee, Scotland. Group of Prof. MAJ. Ferguson. Research project: " Structure and biosynthesis of glycoconjugates in trypanosomatid parasites".
1988-1992	PhD thesis at the Institute of Biochemistry, University of Lausanne, Switzerland. Thesis directors: Dr C. Bordier and Prof. J. Mauë l. Subject: "S tructural and enzymatic characterization of the surface metalloprotease of *Leishmania*"
1984-1988	Licence in Biological Sciences (with one year each biochemistry and organic chemistry certificates), University of Lausanne.
1980-1983	Federal Certificate of Maturity (scientific), Yverdon, Switzerland.

Award

2005	Serono Young Investigator Award for the best recent biotechnology discovery/invention in the Lake of Geneva region

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EXHIBIT B

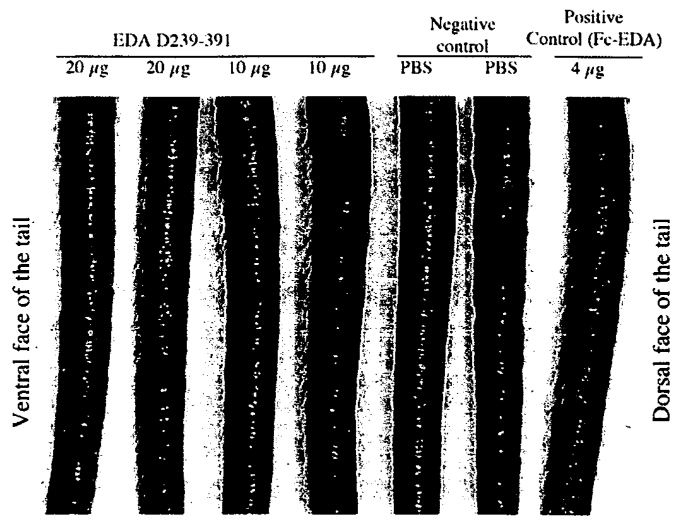

FIG. 1

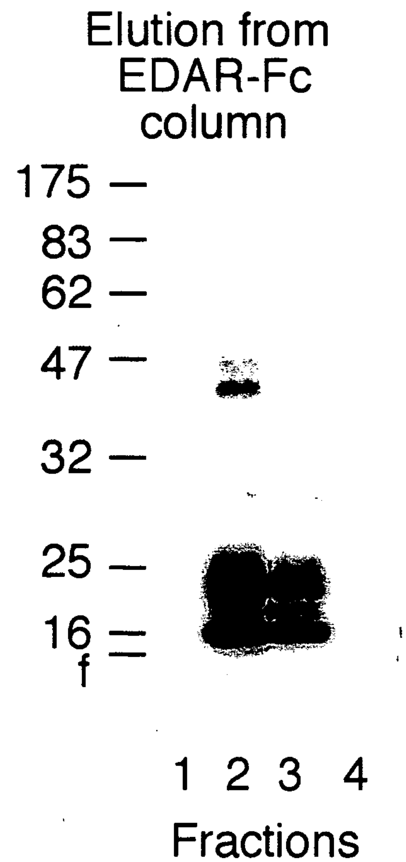

FIG. 2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Zonana et al.
Application No. 09/729,658
Filed: December 4, 2000
Confirmation No. 3101
For: HYPOHIDROTIC ECTODERMAL DYSPLASIA GENES AND PROTEINS
Examiner: Maria Marvich, Ph.D.
Art Unit: 1636
Attorney Reference No. 6907-55924-01

COMMISSIONER FOR PATENTS
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

1. I, Dr. Pascal Schneider, am an Assistant Professor in the Department of Biochemistry at the University of Lausanne, in Switzerland. I have over 10 years of molecular biology experience, and over 4 years of experience in the field of Ectodysplasin A (Eda). I am also a co-author of the Gaide and Schneider article (*Nat. Med.* 9:614, 2003). A copy of my CV is attached as Exhibit A.

2. I have read and understand relevant portions of the above-referenced patent application, including the pending claims, and relevant portions of the Office action dated February 14, 2005.

3. *Tabby* mice are the accepted model of human ectodermal dysplasia. *Tabby* mice share many symptoms with human patients because both X-linked hypohidrotic ectodermal dysplasia and *Tabby* phenotypes are caused by mutations of the syntenic Ectodysplasin A (Eda) gene on chromosome X. Therefore, evidence of success of treatment in the *Tabby* mouse is accepted by me and other persons of skill in this field to correlate with results that can be obtained in humans.

4. The method disclosed in the above-referenced patent application has an important role in treating ectodermal disorders, such as disorders that decrease or inhibit hair, tooth or sweat gland development. For example, the method of the pending claims allows one to increased development

of hair follicles, teeth or sweat glands by increasing EDA1-II activity, such as by administration of an EDA1-II protein (or variant or fragment thereof that retains EDA1-II activity).

5. It is my understanding that in the Office action of February 14, 2005, all of the pending claims, which concern a method of increasing hair follicle, tooth, or sweat glad development, were rejected as not sufficiently enabled by the specification. As shown in FIG. 1 (Exhibit B), results obtained using methods disclosed in the present application demonstrate that EDA1-II proteins can be administered to a subject to increase hair growth. Therefore, the methods disclosed in the present application have been shown by my laboratory to work as described.

6. To demonstrate that increasing EDA1-II biological activity can increase development of ectodermal structures such as hair, the method disclosed in the present application was used to administer an EDA1-II peptide fragment (amino acids 239-391 of EDA1-II) to *Tabby* mice as described in the paragraphs below.

7. The EDA1-II fragment 239-391 was produced in CHO cells using standard molecular biology methods. Briefly, expression constructs containing the human EDA1-II fragment 239-391 were cloned into the PCR3 mammalian expression vector (Invitrogen) using standard molecular biology techniques. The sequence encoding the human EDA1-II protein fragment (amino acids 239-391) was cloned at the 3' of a signal peptide from heamaglutinin (HA signal). The HA signal peptide is removed in the process of secretion, resulting in a mature protein that is a soluble version of human EDA1-II starting at amino acid residue Asp239 that does not contain any non-EDA1-II sequence. CHO cells were transfected with 1.5 µg of plasmid plus 0.5 µg of pEGFP tracer plasmid mixed with 10 µl of Polyfect (Qiagen), according to the manufacturer's instructions. Resulting clones selected with G418 were isolated and expanded. EDA1-II fragment 239-391 secreted into the supernatant was collected after 10 days and subjected to immunoprecipitation followed by anti-EDA Western blotting to confirm expression. For the purification of EDA1-II fragment 239-391, 2 mg of EDAR-Fc was coupled to a 1 ml HiTrap NHS-Sepharose column according to the manufacturer's instructions. Combined elutions of 5 purifications were concentrated to 100 µl in an Amicon Ultra filter device (cut off 10000 Da). Protein concentration was estimated by Western blotting using known amounts of Fc-EDA-1611 protein that had been cleaved to completion with Prescission protease. As Western blot showing the resulting purified EDA1-II fragment 239-391 is shown in

FIG. 2 (Exhibit B). The EDA1-II fragment 239-391 migrates as a doublet, representing N-glycosylated and unglycosylated EDA1-II, respectively.

8. The purified EDA1-II fragment 239-391 was injected intraperitoneally in newborn *Tabby* mice. Homozygous female and hemizygous male *Tabby* mice (Jackson Laboratories, 000314) were injected intraperitoneally at day 1 after birth with a maximal volume of 20 μl using a 0.5 ml syringe (U-100 Insulin 0.5 ml, Becton Dickinson). The amount of protein administered was 10 or 20 µg (about 10-20 mg/kg). Fc-EDA (described in Gaide and Schneider, *Nat. Med.* 9:614, 2003; referenced in the Office action) was used as a positive control. Photography of tail hairs were performed 2.5 weeks post injection.

9. As shown in FIG. 2 (Exhibit B), EDA1-II fragment 239-391 displays biological activity *in vivo* and induces hair formation in *Tabby* mice. At 2.5 weeks post-injection, mice displayed numerous hairs on the tail, particularly of the ventral face. Although this reversion was less marked than that observed with smaller amounts of Fc-EDA, it is still significant compared to the control *Tabby* mice that received only PBS. In PBS-treated animals, the tail is entirely devoid of hair, and the structure of the skin is altered (FIG. 2). In conclusion, we have generated a fragment of EDA1-II composed exclusively of wild type human EDA1-II sequence and that is able to induce formation of hair on the tail of EDA-deficient animals. This provides further evidence of the role of EDA1-II for the treatment of ectodermal disorders such as X-linked hypohidrotic ectodermal dysplasia.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

P. Schneider
Dr. Pascal Schneider

April 14th 2005
Date